

## Machine Translation of JP05-000945

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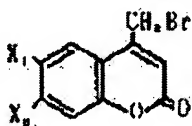
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### (54) CARCINOSTATIC AGENT

(57)Abstract:

PURPOSE: To obtain a carcinostatic agent having excellent carcinostatic action, free from side effect and useful for the inhibition of proliferation of cancer cell by using a specific coumarin compound as an active component.

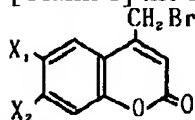
CONSTITUTION: The objective carcinostatic agent contains a coumarin compound of formula (X1 and X2 are OCH3, OH or H provided that both of X1 and X2 are not H at the same time) (e.g. 4-bromomethyl-6,7-dimethoxycoumarin or 4-bromomethyl-6-methoxycoumarin) as an active component. The carcinostatic agent is preferably administered at a daily dose of 1mg to about 10g for adult.



### CLAIMS

[Claim(s)]

[Claim 1] the following general-formula-izing 1 -- [Formula 1]



It is the anticancer agent which makes an active principle the coumarin compound expressed

with (X1 and X2 are either -OCH3, -OH or -H among a formula, and neither X1 nor X2 take -H).  
[0001]

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## DETAILED DESCRIPTION

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[Detailed Description of the Invention]

[Industrial Application] This invention relates to the anticancer agent for checking growth of a cancer cell.

[0002]

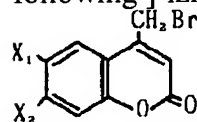
[Description of the Prior Art] In the field of cancer chemotherapy, the compound of the former many is compounded and studied and the thing of a certain is actually used in clinical. However, it is becoming a clinical application top problem as it cannot say that the effectiveness is not necessarily enough to the cancer of various classes seen in clinical and the resistance phenomenon of a cancer cell over those drugs becomes clear in recent years. The new shelf matter which has the carcinostatic effectiveness under this situation is always called for. That is, the effective matter is called for from the cancer which conquers the resistance phenomenon over the existing anticancer agent, and cannot demonstrate effectiveness sufficient in the existing anticancer agent.

[0003]

[Problem(s) to be Solved by the Invention] This invention is for solving the above-mentioned technical problem, and the purpose of this invention is to offer the new anticancer agent which consists of a compound which has the outstanding carcinostatic operation.

[0004]

[Means for Solving the Problem] this invention -- as an anticancer agent -- the general-formula[ following ]-izing 2 -- [Formula 2]



The coumarin compound expressed with (X1 and X2 are either -OCH3, -OH or -H among a formula, and neither X1 nor X2 take -H) is contained as an active principle.

[0005] As a typical thing of the above-mentioned coumarin compound in this invention, 4-bromomethyl -6, 7-dimethoxy coumarin, a 4-bromomethyl-6-methoxy coumarin, a 4-bromomethyl-7-methoxy coumarin, 4-bromomethyl -6, 7-dihydroxy coumarin, 4-bromomethyl-6-hydroxycoumarin, 4-bromomethyl-7-hydroxycoumarin, etc. can be illustrated. Each of these compounds is known compounds, it is low toxicity, and fifty percent lethal dose (intraperitoneal administration) to a mouse is 100 or more mg/kg.

[0006] When using the above-mentioned compound as an anticancer agent, it can manufacture medicine and use for a tablet, a capsule, a fine grain agent, syrups, a suppository, an ointment, injections, etc. with taking orally, \*\*\*\*, or any parenteral gestalt of administration, for example. In this case, inactive support, for example, a crystalline cellulose, gelatin, a lactose, starch, magnesium stearate, talc, a vegetable property, animal fat and an oil, gum, a polyalkylene glycol, etc. can be used as support of pharmaceutical preparation pharmacologically [ taking orally, \*\*\*\*, the organic or inorganic solid-state suitable for prescribing a medicine for the patient

parenterally, or a liquid ]. To such support, in 0.1 - 200% of range, the drugs of this invention can select the above-mentioned compound suitably, and it can be used for them. Moreover, the drugs of this invention can also be used, mixing with the physic of other same drugs or others. [0007] The anticancer agent of this invention is prescribed for the patient with a dose which is attained without accompanying a desired operation by the remarkable side effect, and generally, its range of 1mg - 10g per adult day is desirable, and it can be suitably prescribed for the patient in 1 - several steps per day in the toxic range not appearing.

[0008]

[Example]

The carcinostatic operation over a mouse experiment tumor cell was investigated using the coumarin compound shown in the carcinostatic operation test report 1.

[0009] The mouse leukemic cell L1210 or the mouse skin black tumor cell B16 was put into the Eagle's minimum essential medium(MEM)-10% fetal-calf-serum culture medium, and what was cultivated under the temperature of 37 degrees C was used in the incubator which contains the carbon dioxide gas of concentration 5%. This cell was wound around the 96 hole multi-plate (falcon company make) by 1x10<sup>4</sup>/100microl / well, and it cultivated at 37 degrees C for 24 hours. Said coumarin compound was dissolved in dimethyl sulfoxide, it diluted with the above-mentioned culture medium, and the dilution liquid of various concentration was added to the well of the multi-plate after said culture every [ 100micro / l ]. After cultivating this at 37 more degrees C for 20 hours, the thymidine solution (37K becquerel) which carried out the indicator by 3H (tritium) was added every [ 20micro / l ]. 4 hours after, DNA of a cell was caught to the glass filter by the cell harvester, and the incorporated activity was measured. The growth inhibition operation considered as control what did not add a coumarin compound, and asked for it compared with this control as concentration (ED50muM) of the coumarin compound to which incorporation of the tritium to DNA can be reduced 50%. These results were shown in Table 1.

[0010] It turns out that the coumarin compound with which the 4th place was permuted by the bromomethyl radical, and the 6 or 7th place was permuted by the methoxy group or the hydroxy group from this result has a strong cancer cell growth inhibition operation, i.e., a carcinostatic operation.

[0011] Example 14-bromomethyl -6 and 7-dimethoxy coumarin 200mg and 900mg of sodium chlorides are set as the dissolution, the whole quantity is set to 100ml at distilled water for injection, subsequently sterilization filtration is carried out, and it fills up and \*\*\*\* at a time in the ampul for 5ml at 5ml. This is considered as intramuscular injection or intravenous injection.

[0012] Example 24-bromomethyl-7-methoxy coumarin 10mg, 300mg [ of lactoses ], and starch 30mg and 10mg of magnesium stearates are cast to a tablet with a conventional method as an ingredient for one lock. Glycocalyx may be attached if needed.

[0013]

[Effect of the Invention] As explained above, the compound of this invention has the clearly excellent carcinostatic operation, and has practical use value \*\*\*\*\* as an anticancer agent.

[Table 1]

化 合 物 名	細胞増殖阻止ED50( $\mu$ M)	
	L1210	B16
4-ブロモメチル-6,7- ジメトキシクマリン	0.25	3.1
4-ブロモメチル-7- メトキシクマリン	0.45	4.6
4-メチル-6,7- ジメトキシクマリン	150	83
4-メチル-7- メトキシクマリン	>500	95